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HMG20A as regulator of β-cells adaptive response by stimulation of mitochondrial activity and protection from senescence

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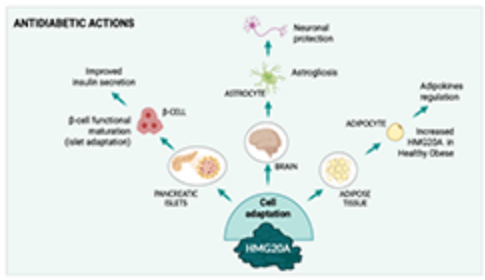
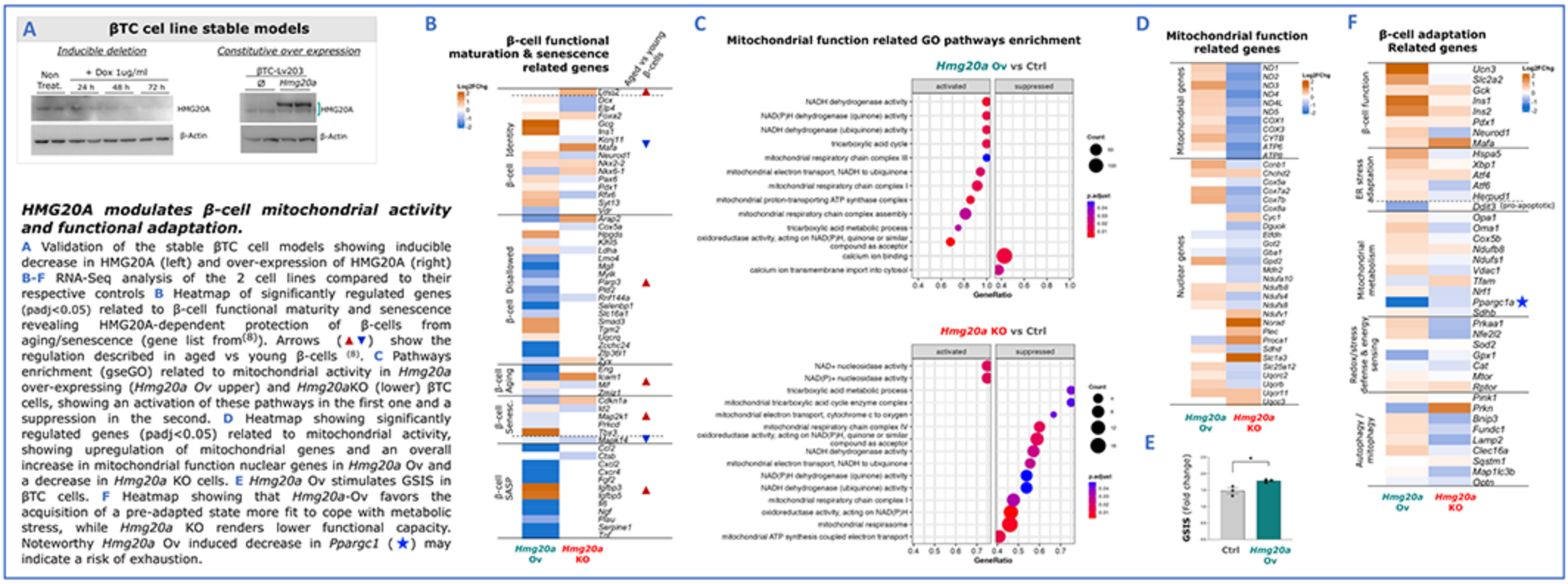
Introduction & Objective



The association of polymorphisms in the chromatin binding factor HMG20A with type 2 diabetes (T2D) and gestational diabetes (GD) [1-3], together with its decreased expression in islets from T2D donors [4], has revealed a new target for the development of novel therapies for the treatment of diabetes. Our previous studies (Figure) demonstrated that HMG20A: i) is required for islet β-cell functional maturity and its silencing blunts GSIS [4]; ii) mediates astrogliosis protective effect on neurons [5]; and iii) is significatively increased in adipocytes from subcutaneous fat from obese non-diabetic individuals when compared to obese diabetic, correlating with an increase in adiponectin. HMG20A mechanism of action is through its interaction with LSD1-CoREST and PHF14 complexes and its antagonist heterodimerization with HMG20B [6-7]. However, HMG20A also harbors a DNA binding domain that allows its direct interaction with DNA.

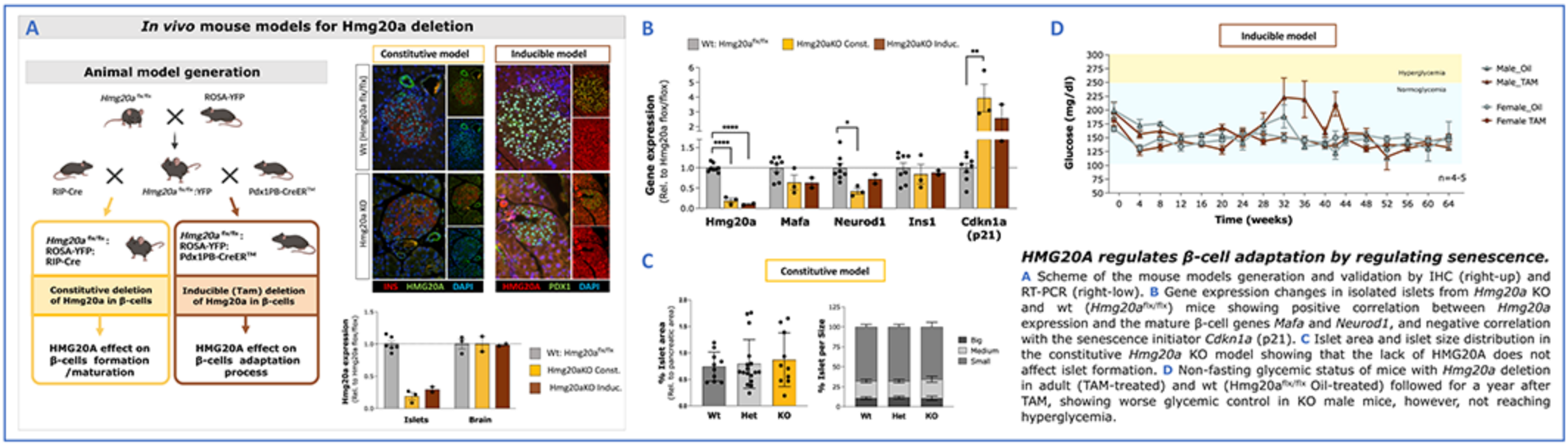
Objective: To further understand HMG20A mode of action on islet health and performance, we have both deleted and overexpressed *Hmg20a* in the mouse βTC cell line and generated two mouse models with *Hmg20a* deletion in β-cells: i) constitutive deletion to study HMG20A effect on islet formation and ii) Tam-inducible deletion to characterize HMG20A effect in islet adaptation during aging or in an obesity-induced hyperglycemia model (DiO).

Results



HMG20A modulates β-cell mitochondrial activity and functional adaptation.

A Validation of the stable βTC cell models showing inducible decrease in HMG20A (left) and over-expression of HMG20A (right) **B-F** RNA-Seq analysis of the 2 cell lines compared to their respective controls **B** Heatmap of significantly regulated genes (padj<0.05) related to β-cell functional maturity and senescence revealing HMG20A-dependent protection of β-cells from aging/senescence (gene list from[8]). Arrows (▲▼) show the regulation described in aged vs young β-cells [8]. **C** Pathways enrichment (gseGO) related to mitochondrial activity in *Hmg20a* over-expressing (*Hmg20a Ov* upper) and *Hmg20a*KO (lower) βTC cells, showing an activation of these pathways in the first one and a suppression in the second. **D** Heatmap showing significantly regulated genes (padj<0.05) related to mitochondrial activity, showing upregulation of mitochondrial genes and an overall increase in mitochondrial function nuclear genes in *Hmg20a* Ov and a decrease in *Hmg20a* KO cells. **E** *Hmg20a* Ov stimulates GSIS in βTC cells. **F** Heatmap showing that *Hmg20a*-Ov favors the acquisition of a pre-adapted state more fit to cope with metabolic stress, while *Hmg20a* KO renders lower functional capacity. Noteworthy *Hmg20a* Ov induced decrease in *Ppargc1* (★) may indicate a risk of exhaustion.



HMG20A regulates β-cell adaptation by regulating senescence.

A Scheme of the mouse models generation and validation by IHC (right-up) and RT-PCR (right-low). **B** Gene expression changes in isolated islets from *Hmg20a* KO and wt (*Hmg20a*$^{fl/fl}$) mice showing positive correlation between *Hmg20a* expression and the mature β-cell genes *Mafa* and *Neurod1*, and negative correlation with the senescence initiator *Cdkn1a* (p21). **C** Islet area and islet size distribution in the constitutive *Hmg20a* KO model showing that the lack of HMG20A does not affect islet formation. **D** Non-fasting glycemic status of mice with *Hmg20a* deletion in adult (TAM-treated) and wt (Hmg20a$^{fl/fl}$ Oil-treated) followed for a year after TAM, showing worse glycemic control in KO male mice, however, not reaching hyperglycemia.

Summary & Conclusions

HMG20A promotes the expression of β-cell identity genes, while decreases β-cell disallowed genes as well as aging and senescence genes. As expected, based on the established link between senescence and impaired mitochondrial function, these gene-changes correlate with enhanced mitochondrial function related genes. Moreover, HMG20A favors the acquisition of a pre-adapted state in the islets, more fit to cope with metabolic stress. *In vivo*, the lack of HMG20A, despite no effects on islet organogenesis, worsens the glycemic control in male mice, supporting its involvement in islet adaptive responses.

HMG20A regulates β-cell adaptive response to increased insulin demand by promoting β-cell functional maturation and protecting against senescence, emerging as a promising target for innovative antidiabetic therapies.

References

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Acknowledgements: